REMARKS

Claims 1-24, 28-31 and 36 are pending and rejected in this application. Applicants amend claims 1, 4-24, 28-31, and 36, and cancel claims 2, and 3, without prejudice or disclaimer. Applicant also amends withdrawn process claim 32 to retain consistency with the product claims from which it depends. With entry of this amendment claims 1, 4-24, 28-31, and 36 are under consideration.

No new matter is presented by way of the amendments to the claims. Amendments to claims 1, 4-24, 28-32, and 36 are presented to more closely conform the claims to US practice. Applicants amend claim 1 to more clearly articulate certain aspects of the subject matter. Support for the amendments is found throughout the specification and claims as originally submitted. Accordingly, Applicants request entry of the amendments and reconsideration of the claims in light of following remarks.

Corrections to the specification

Applicants herewith submit a substitute specification reflecting corrections and amendments requested by the Examiner. However, Applicants note that the first paragraph of the specification was amended in a preliminary amendment dated 4 May 2005 to incorporate reference to PCT/EP2003/012402 as follows: This application is a 371 application of PCT/EP2003/012402. Accordingly, this paragraph is reflected in the substitute specification, but is shown without markings on the marked-up version.

Claims 1-24, 28-31 and 36 point out and distinctly claim the subject matter which Applicants regards as the invention.

Claims 1-24, 28-31 and 36 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

More particularly, claim 1 and claims dependent therefrom, stand rejected because the language "wherein the HIV envelope protein is adapted to reduce or prevent glycosylation in a mammalian cell" is deemed by the Examiner to be unclear. This language does not appear in amended claim 1, rendering the rejection moot.

Claims 7, 9, 11, 14 and 20 stand rejected on the grounds that these claims the arrangement of recited elements is not clear. Applicants herein amend these claims to indicate the 5′ to 3′ arrangement of the elements.

Claim 16 stands rejected on the grounds that the phrasing is allegedly unclear. Applicants herein amend the claims as suggested by the Examiner to enhance clarity.

In view of the aforementioned amendments, Applicants believe that the claims are clear and definite as required by 35 U.S.C. § 112, second paragraph, and respectfully request that these rejections be withdrawn.

Claims 1, 4-24, 28-31 and 36 are novel

Claims 1, 2, 4, 5, 12, 13, 17, 18, 21, 22, 28-31 and 36 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Nabel *et al.* (WO 02/32943 ; hereinafter "Nabel"). To the extent that these rejections are maintained with respect to the amended claims, Applicants traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Claim 1 (as amended) is directed to: "[a] pharmaceutical composition comprising a polynucleotide that comprises a sequence encoding an HIV gp120 envelope protein lacking a functional secretion signal operably linked to a heterologous promoter, wherein the HIV gp120 envelope protein is substantially non-glycosylated when expressed in a mammalian target cell, and at least one pharmaceutically acceptable excipient, diluent, and/or carrier." The Examiner alleges that Nabel discloses "DNA vectors comprising sequences that encode an HIV Env that is non-glycosylated," as well as "HIV Env fused to another HIV gene such as Nef." (citations omitted) The Examiner also alleges that Nabel teaches compositions including the vectors and carriers and adjuvants, as well as methods for their administration.

However, the Examiner does not suggest that Nabel teaches a gp120 envelope protein lacking a functional secretion signal. Furthermore, nothing in the cited portions of Nabel (*e.g.*, pages 43, 45 and 46) discloses any variant of gp120 Env that lacks a functional signal sequence. Rather, Nabel discloses "mutants in which conserved N-linked glycosylation sites were eliminated by site-directed mutagenesis of HIV Env" (*e.g.*, p. 43, lines 29-30) and "a series of internal mutations designed to replace the cleavage site (C), the fusion domain (F), and the interspace (I) between the two heptad repast all on a backbone of COOH-terminal truncations to expose the core protein of the viral membrane fusion protein Env..." (*e.g.*, p. 37, lines 16-20). The various constructs appear to be depicted schematically in Figure I. As shown in Figure I, all of the disclosed constructs include the N-terminal signal sequence of the native gp160 (gp120) protein.

Because Nabel does not either expressly or inherently disclose a pharmaceutical composition comprising a polynucleotide that comprises a sequence encoding an HIV gp120 envelope protein lacking a functional secretion signal, this reference cannot anticipate claim 1, and claims dependent therefrom. Applicants respectfully request that this rejection be withdrawn.

Claims 1, 4-24, 28-31 and 36 are non-obvious

Claim 3 stands rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nabel in combination with Botarelli *et al.* (*Journal of Immunology* 147:3128-3132, 1991; "Botarelli"). Cancellation of claim 3 renders this rejection moot. However, to the extent that the rejection is maintained with respect to the amended claims, Applicants traverse.

Under 35 U.S.C. § 103, a patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. In view of the Supreme Court's recent decision in *KSR Int'l v. Teleflex Inc.*, the Examiner is required "to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum to Technology Center Directors on

the subject of the Supreme Court decision on *KSF Int'l Co., v. Teleflex, Inc.*, dated May 03, 2007. Thus, A proper rejection under 35 USC § 103 requires that the Examiner 1) identify prior art that differs from the claimed subject matter only in a way that would have been obvious at the time the invention was made, and 2) to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

As discussed above, Nabel differs from the subject claims in that the constructs and compositions disclosed by Nabel encode mutant gp120 Env proteins in which conserved N-linked glycosylation sites were eliminated. The compositions disclosed by Nabel all possess a functional secretion signal.

The Examiner alleges (page 7 of the Office Action) that Botarelli teaches a non-glycosylated form of HIV gp120 that "was produced by removing the signal sequences," and that "Botarelli *et al.* states that [t]he lack of signal sequence prevents passage through the secretory pathway and addition of carbohydrates." The Examiner contends that:

> It would have been obvious to one of ordinary skill in the art to modify the polynucleotides taught by Nabel et al. to use HIV env. Sequences lacking a secretory signal sequence to produced non-glycosylated HIV Env. One would have been motivated to do so, given the suggestion by Botarelli et al. that glycosylation residues on gp120 can function as hindering structures that limit antigen recognition by T-lymphocytes. There would have been a reasonable expectation of success, given the fact that it is well known that the removal of the secretory signal sequence bypasses the secretory pathway and the addition of carbohydrates, and that others have successfully produced non-glycosylated proteins by removing the secretory signal sequence. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art oat the time the invention was made.
> (p. 7-8, of Office Action)

Applicants respectfully disagree.

As a preliminary matter, although Nabel discloses DNA vaccines including polynucleotides that encode non-glycosylated Env protein (*i.e.*, with mutations in the highly conserved N-linked glycosylation sites), Nabel cannot fairly be viewed as teaching that such polynucleotides are particularly favorable vaccines, or as leading a skilled practitioner to seek additional polynucleotide compositions that encode non-glycosylated Env proteins, such as the HIV gp120 envelope protein lacking a functional secretion signal of claim 1. Instead, Nabel teaches that "[m]utations in highly conserved N-linked glycosylation sites did not

significantly alter humoral or cellular immune response to native Env." (page 45, lines 31-33), and that "[e]limination of conserved glycosylation sites did not substantially enhance humoral or CTL immunity." Indeed, Nabel concludes that "glycosylation mutants are unlikely to prove helpful" with DNA vaccination (*see*, page 46, lines 22-24). Thus, rather than teaching a skilled practitioner to use a DNA vaccine encoding a non-glycosylated gp120, Nabel teaches the skilled practitioner to eschew a DNA vaccine encoding a non-glycosylated gp120 in favor of alternatives "with deletions in the cleavage site, fusion domain, and a region between the heptad repeats."

Even if the skilled practitioner ignored the teaching by Nabel to use other polynucleotides rather than those that encoded non-glycosylated Env proteins, it would not have been obvious to a skilled practitioner to modify Nabel's constructs by eliminating the secretory signal (and leaving the glycosylation sites intact). The Examiner alleges that it would be obvious to do so because Botarelli suggests "that glycosylation residues on gp120 can function as hindering structures that limit antigen recongnition by T-lymphocytes." From this, the Examiner extrapolates that one of skill in the art would be motivated to produce polynucleotides that encode non-glycosylated Env proteins produced by removing the secretory signal. However, to arrive at this conclusion requires taking Botarelli's suggestion (cited above) out of context. In fact, Botarelli discloses that immunization with the non-glycosylated Env protein produced in yeast elicits an immune response in which a significant proportion of the T cells *are unable to recognize native glycosylated gp120* (as expressed during virus infection). Botarelli concludes: "Altogether these data suggest that N-linked glycosylation may be responsible for the inability of T cells specific for nonglycosylated gp120 to recognize glycosylated gp120." (p. 3129, second column, third paragraph). One of skill in the art would understand this to mean that glycosylation of the native protein interferes with recognition by T cells elicited by immunization with the non-glycosylated protein, not that immunization with a non-glycosylated protein elicited a more favorable response than a glycosylated form of Env protein antigen. Thus, Botarelli cannot be viewed as providing a motivation to vaccinate with a non-glycosylated form of Env any more than can Nabel. Nor can Botarelli be viewed as providing a reasonable expectation that such a vaccine would be successful for the reasons discussed above.

Not only does Botarelli not provide any motivation or suggestion for modifying the teachings of Nabel to arrive at the claimed subject matter, but a skilled practitioner would be unlikely to seek direction for modifying DNA vaccines in the teachings of Botarelli, because the compositions disclosed by Botarelli are fundamentally different. Botarelli discloses polynucleotides that are useful for the production of protein (HIV Env) antigens. At no point does Botarelli teach that the disclosed polynucleotides can be used in pharmaceutical compositions, *i.e.*, as DNA vaccines.

Indeed, it is unlikely that one of skill would have looked to the polynucleotides of Botarelli as even being suitable for administration in a pharmaceutical composition. In the first place, the constructs of Botarelli are designed for expression in yeast. Accordingly, the polynucleotide sequence encoding the Env polypeptide is operably linked to a yeast promoter (*e.g.*, yeast pyruvate kinase (*pyk*), glyceraldehydes-3-phosphate dehydrogenase (GAPDH)). (Details of the constructs and production are found in Barr *et al.*, *Vaccine* 5:90-101, 1987. reference 6 of Botarelli, appended herewith). One of skill in the art would not view either of these yeast promoters as being favorable for expressing a protein *in vivo* in a mammalian (*e.g.*, human cell). Second, as pointed out by the Examiner, the constructs of Botarelli produced proteins that could not be secreted by the yeast cells in which they were produced. In order to obtain the protein antigens, the yeast cells were harvested and the cells disrupted with glass beads, prior to solubilizing and denaturing in SDS, and then concentrating and purifying the expressed Env proteins. This production process, and indeed the recombinant production of protein antigens is wholly non-analogous to DNA vaccines, and one of ordinary skill in the art would not look to recombinant production in yeast to guide the modification of polynucleotide vaccines because the recovery method is wholly inapplicable. Furthermore, Nabel teaches consistently that expression of the Env protein *in vivo* in the host cell is important, and discloses that the variant of Env that "induced the greatest antibody response, is released in a soluble form." (*see*, p. 46, lines 9-10). Thus, a practitioner of ordinary skill in the art would not have found it obvious to to use a polynucleotide that encoded an Env protein that could not be secreted by the host cell to produce a non-glycosylated antigen *in vivo* in the context of a DNA vaccine.

Rather, as stated in the instant specification, Applicants surprisingly discovered that in the context of a DNA vaccine, "a DNA vector expressing gp120 without a secretion signal and which is thus not glycosylated or secreted from the cell is a more effective stimulator of CTL responses than a DNA vector expressing gp120 with its native secretion signal." (page 7, lines 7-10, of the instant specification). Applicants respectfully remind the Examiner that it is impermissible to use "knowledge gleaned only from applicant's disclosure" in making an obviousness rejection. *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Given the cumulative teaching in the cited art that would lead a skilled practitioner away from the production of pharmaceutical compositions including polynucleotides that encode an HIV gp120 lacking a secretory signal, it is only Applicants' disclosure that provides the basis for producing the compositions of claim 1 (and claims dependent therefrom).

Claims 15-16 and 23-24 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nabel in combination with Catchpole (WO 02/36792) and Farina *et al.*, and Roy *et al.*, respectively. Nothing in Catchpole, Farina or Roy remedies the deficiencies of Nabel in combination with Botarelli. Thus, these combinations of references cannot render obvious claims 15-16 and 23-24, which incorporate all of the limitations of amended claim 1 (*e.g.*, the limitations of original claim 3).

Claims 1, 2, 4 and 12 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Jiang *et al.* (*Chinese Journal of Microbiology and Immunology*, 2002, 22:482-484, abstract only) in view of Botarelli. Applicants respectfully submit that the amendments to the claims render this rejection moot.

In view of the foregoing remarks, Applicants submit that the claims are not obvious, and the rejections under 35 U.S.C. § 103(a) should be withdrawn.

Conclusion

On the basis of the amendments and remarks above, Applicants believe that the claims are now in condition for allowance. In the event that additional substantive issues remain, Applicants respectfully request that the Examiner contact their undersigned attorney

to arrange a telephonic interview prior to the preparation of any further written action. Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification.

Respectfully submitted,

Gwynedd Warren
Attorney for Applicant
Registration No. 45,200

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-7241
Facsimile (610) 270-5090
GW:\applications\P apps\PG5023\ROA.doc